

PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Variations in outcomes by residential location for women with breast cancer: a systematic review
AUTHORS	Dasgupta, Paramita; Baade, Peter; Youlden, Danny; Garvey, Gail; Aitken, Joanne; Wallington, Isabella; Chynoweth, Jennifer; Zorbas, Helen; Youl, Philippa

VERSION 1 – REVIEW

REVIEWER	Howard P. Greenwald University of Southern California, Los Angeles, United States of America
REVIEW RETURNED	04-Sep-2017

GENERAL COMMENTS	<p>Review: Variations in outcomes by residential location for women with breast cancer: a systematic review.</p> <p>General:</p> <ol style="list-style-type: none">1. It is very difficult to grasp what literature actually says without some standard tabular presentation and/or graphics. A series of very burdensome tables follow the text, and the highlights of these must be clearly presented in simpler tables.2. Comment should be more (or made more prominently) about the artificial impact of early detection on survival. It is well known that earlier identification of cancer in a patients leads to apparently longer survival time not for any pathophysiological reason but merely because the presence of disease has been known for a longer time. "Stage" does not capture this spurious extension, and the literature cited should be scanned to see whether this has been taken into consideration.3. In addition, the authors should comment in text on the periods over which mortality was followed. Although breast cancer is often successfully treated at initial diagnosis it tends to recur and modelling of survival requires followup considerably longer than the five years often cited as an index of cure.4. Much is made in the article about detection via screening and its desirability supported by reference to an Australian authority. Yet, mammography is highly controversial, and important studies cite resulting, adverse effects, and characterize increase in life expectancy as problematical. Thus, there needs to be more detailed discussion of what screening may or may not contribute in
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	<p>consideration of the findings cited in the literature review.</p> <p>5. The article rightly cites the complex interactions between rural location and numerous socio-economic, service availability, and other factors. But preceding this appropriate disclaimer, it is reported that both relative poverty and rural residence contribute to mortality, and that rural residence and poverty are related. Special attention needs to be paid to what the literature may say about the degree to which difference in treatment and mortality between non-rural and rural women may be explained by difference in income. (ref. pg. 8, line 31).</p> <p>6. The authors assert that the great variation in studies identified (and/or their settings) preclude meta-analysis. Not performing a meta-analysis results in a somewhat impressionistic paper, with many seemingly contradictory findings reported from study to study. A more effective paper could be written if the authors applied stronger selection/rejection criteria, or selected an appropriate subset of studies for meta-analysis, and in fact performed one.</p> <p>7. It is concluded that women with breast cancer should be treated by multidisciplinary team. I have may have missed this but how is this supported by evidence? Do the studies cited actually identify multidisciplinary team treatment (or consultation) as a predictor of survival, and if so, how is team treatment measured?</p> <p>8. Supplementary files make up 2/3 of the submission and most could be deleted, briefly summarized, or offered to be sent on request.</p> <p>Other:</p> <p>Pg.10. Very interesting findings: non-metropolitan women were at least five times more likely to have a mastectomy than metropolitan women. "Two studies based on the National Breast Cancer Audit Database reported that non-metropolitan women were up to 20% less likely to receive adjuvant radiotherapy than metropolitan women.^{42 61} Moreover women residing in areas lacking radiotherapy facilities had a higher likelihood (23%) of not receiving radiotherapy than those from regions with such facilities.⁶¹" suggests poverty is the issue.</p> <p>Pg. 12, line 39. "...good evidence that poorer breast cancer survival for nonmetropolitan women reflects more advanced disease at diagnosis, greater comorbidities and treatment-related factors." Authors should cite sample of outstanding studies for these assertions.</p> <p>Pg. 13 multidisciplinary team is this supported by evidence?</p> <p>Pg. 14. Say what "Cancer Australia" is when the agency is first cited in the text.</p> <p>Pg. 14. Good paragraph but could more be found in this article's data base to move toward resolution of issues in the following paragraph:</p> <p>On an international scale, inequities in access to specialised care⁸¹⁻</p>
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	83 and geographical variations across the breast cancer continuum including screening,7 stage at diagnosis9 97 and patterns of care8 86 97-102 are well documented. There is widespread consensus that these variations reflect a combination of socio-economic, demographic and environmental factors including geography, comorbidities, access, treatment and stage at diagnosis that defy easy solutions.7-9 82 83 97 101 The persistence of such inequities even for universal (publicly-funded) health-care systems7 82 97 99 102 highlights the complexity of the underlying issues."
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REVIEWER	Rob Olson BC Cancer Agency, Canada
REVIEW RETURNED	04-Nov-2017

GENERAL COMMENTS	<p>1) It is not clear why this review had to be limited to an Australian setting, and I would prefer that it was not limited in this way. Certainly a large proportion of research has been done in Australia, but there are important studies from elsewhere that are interesting to this general area of research: rural vs urban outcomes in breast cancer.</p> <p>2) in the discussion, the rationale for radiotherapy is correctly (in part) described to reduce local recurrence, but the potential survival benefit of radiotherapy is not fully described or possibly associated with differences in outcomes. This should be added, as others (e.g. BC, Canada) have shown nodal radiotherapy is used less frequently in small, and rural locations, which could result in lower survival.</p> <p>3) a better description of socioeconomic differences across Australia would be helpful for non-local readers.</p> <p>4) figures summarizing the differences in survival, screening rate, mastectomy use, adjuvant local radiotherapy, adjuvant loco-regional radiotherapy, adjuvant chemotherapy, adjuvant hormonal therapy use would help the reader get a better overall view of the differences.</p> <p>Ultimately, my biggest concern is the missed opportunity to review outside of Australia. I think the group should consider widening their review to international data sources with rural-urban comparisons.</p>
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VERSION 1 – AUTHOR RESPONSE

Response to Reviewers comments: Manuscript ID bmjopen-2017-019050

- All references given in this document are in the Author, Year format to avoid confusion with the references in the manuscript.
- Please note that all Page Numbers refer to the revised manuscript.

Associate Editor Comments to Author:

1. This is an interesting paper from Australia. It's very well written. My only thought is that the search is old (2015) and needs updating, if possible. Reviewer Olson does make a good point that background about the SE context in Australia would help. The idea of widening the search beyond Australia is a bit unrealistic at this stage.

Authors' response: The review has been updated with systematic searches repeated to cover all articles published from 1/1/1990 to 24/11/2017.

Additional changes to reflect this interpretation have been made to the manuscript. Given the number of changes made, these are indicated below in terms of their location in the manuscript as outlined below:

Abstract: Page 2

Methods:

Page 5, Literature searches

Results:

Page 7, Study selection, Study characteristics

Pages 8, Key findings

Pages 8-9 Survival Outcomes

Pages 9 Tumour characteristics

Page 9 Screening rate

Page 10 Rescreening

Pages 10-11 Clinical management

Page 11 Recommended clinical management

The Discussion, Tables and Figure 1 have also been modified accordingly

Additional information on the socioeconomic context for Australia has also been added to Introduction (Page 4). Please see response to Comment #17

Reviewer: 1

2. It is very difficult to grasp what literature actually says without some standard tabular presentation and/or graphics. A series of very burdensome tables follow the text, and the highlights of these must be clearly presented in simpler tables.

Authors' response: We have modified the key tables (Tables 3-6) to clearly summarize the differences by residential location according to clinical questions within each of the key themes. The original Tables have been retained as Supplementary material.

Additional comment has been added to the Results (Key findings, Page 8):

"Studies are summarized below (Tables 3-6, also Supplementary Appendix 4)"

These Tables are shown on Pages 22 to 26

3. Comment should be more (or made more prominently) about the artificial impact of early detection on survival. It is well known that earlier identification of cancer in a patients leads to apparently longer survival time not for any pathophysiological reason but merely because the presence of disease has been known for a longer time. "Stage" does not capture this spurious extension, and the literature cited should be scanned to see whether this has been taken into consideration.

Authors' response: We have added the following text to the Discussion (Page 12, Paragraph 2):

"It is possible that these survival patterns are impacted by the lead time caused by mammographic screening; (Welch et al. 2016) while we found only limited evidence that participation in the publicly funded BreastScreen services varies by geographical area, the lack of data on the number of privately screened women precludes an evaluation of actual population-based screening participation and its impact on the observed survival patterns."

4. In addition, the authors should comment in text on the periods over which mortality was followed. Although breast cancer is often successfully treated at initial diagnosis it tends to recur and modelling of survival requires followup considerably longer than the five years often cited as an index of cure.

Authors' response: All but one of the 22 included studies only reported on five-year survival estimates. An additional sentence has been added to the Results (Survival Outcomes, Page 9):

"Most of the 22 included studies focused on medium term survival, with only one (Tracey et al. 2008) following women for longer than five years after their breast cancer diagnosis."

We have also added the following phrase to the second paragraph in the Discussion in relation to the survival patterns (Page 12) “(at least up to five years after diagnosis)”

5. Much is made in the article about detection via screening and its desirability supported by reference to an Australian authority. Yet, mammography is highly controversial, and important studies cite resulting, adverse effects, and characterize increase in life expectancy as problematical. Thus, there needs to be more detailed discussion of what screening may or may not contribute in consideration of the findings cited in the literature review.

Author's response: The focus of this systematic review was on the observed inequalities in breast cancer screening by residential location among women aged 50 to 69; as such a detailed justification of mammographic screening and discussion of its controversies was outside the scope of this review. We have, however, already referred to a recent systematic review by the International Agency for Research on Cancer (IARC) (Lauby-Secretan et al. 2015) that concludes there is sufficient evidence for the efficacy of mammographic screening in reducing breast-cancer mortality for women aged 50 to 69 years.

No changes have been made to the manuscript

6. The article rightly cites the complex interactions between rural location and numerous socio-economic, service availability, and other factors. But preceding this appropriate disclaimer, it is reported that both relative poverty and rural residence contribute to mortality, and that rural residence and poverty are related. Special attention needs to be paid to what the literature may say about the degree to which difference in treatment and mortality between non-rural and rural women may be explained by difference in income. (ref. pg. 8, line 31).

Author's response: Differences between rural and non-rural women are likely to reflect difference in socio-economic characteristics. However, population-based cancer registries in Australia do not collect information on individual measures of socio-economic status such as income or education. (AIHW 2017a)

Hence the included articles cannot comment specifically on the extent to which difference in treatment and survival are explained by differences in individual income.

To avoid confusion, we have modified this paragraph to highlight we are referring to area-level disadvantage, not individual level socioeconomic status (Results, Survival Outcomes, Page 8):

“However, no geographical differential in survival was evident across 11 (Cramb et al. 2012, Dasgupta et al. 2012, Hall et al. 2004, Mitchell et al. 2006, Roder et al. 2012a, Spielsbury et al. 2005, Supramaniam et al. 2014, Taylor 1997, Tracey et al. 2008, Tervonen et al. 2017, Hsieh et al. 2016) of 20 studies that also reported survival estimates after adjustment for various combinations of known survival determinants including demographics, area-level disadvantage, spread of disease, comorbidities and treatment-related factors”

We have added the following clarification re area-level disadvantage to the Discussion (Page 12, Paragraph 2):

“While gaps in the literature limited our ability to draw clear links between identified variations and the drivers of these variations, there was good evidence that poorer breast cancer survival (at least up to five years after diagnosis) for non-metropolitan women reflects more advanced disease at diagnosis, greater comorbidities, treatment-related factors and area-level disadvantage. (Cramb et al. 2012, Dasgupta et al. 2012, Mitchell et al. 2006, Roder et al. 2012a, Spielsbury et al. 2005, Supramaniam et al. 2014, Tracey et al. 2008, Tervonen et al. 2017) ”

Also in the Limitations (Page 15, Paragraph 2):

“While using registry data allows generalizability of findings, such studies cannot comprehensively control for all potential confounders, especially those related to individual-level socio-economic status, clinical or treatment factors, since Australian cancer registries do not routinely collect information on

these measures. (AIHW 2017a) Hence population-based studies can adjust for area-level socio-economic status but not between-persons differences. Only cross-sectional studies, although deemed inferior to population-based studies in terms of representativeness, can collect information on individual-level measures.”

Please also see responses to Comment #17

7. The authors assert that the great variation in studies identified (and/or their settings) preclude meta-analysis. Not performing a meta-analysis results in a somewhat impressionistic paper, with many seemingly contradictory findings reported from study to study. A more effective paper could be written if the authors applied stronger selection/rejection criteria, or selected an appropriate subset of studies for meta-analysis, and in fact performed one.

Author's response: While we understand the restrictions of not performing a meta-analysis, we felt that applying stronger selection/rejection criteria would result in a less representative snapshot of the geographical patterns of breast cancer indicators in Australia. While we were not able to specifically quantify the average magnitude of increase or decrease in likelihood in our study, presenting the evidence for women living in non-metropolitan areas generally having a higher, lower or similar likelihood of a specific indicator is important and novel information.

No changes have been made to the manuscript.

8. It is concluded that women with breast cancer should be treated by multidisciplinary team. I have may have missed this but how is this supported by evidence? Do the studies cited actually identify multidisciplinary team treatment (or consultation) as a predictor of survival, and if so, how is team treatment measured?

Author's response: Additional commentary (with appropriate references) has been added to the Discussion (Page 13):

“Reasons for these variations likely included limited access to oncological services and multidisciplinary care. (Wilcoxon et al. 2011, Breast Cancer Network Australia. 2017) Regional Cancer Centres across Australia and integrated cancer networks were established to improve access to oncological care for regional patients. (Smith 2012, Murphy et al. 2015) However overcoming barriers to multidisciplinary care, considered best practice in breast cancer care, (Senkus et al. 2015, National Institute for Clinical Excellence. 2009, Cancer Council Australia. 2017) in regional areas remains a challenge. Multidisciplinary cancer teams (MDT) are sparse outside metropolitan areas and vary widely in the disciplines represented within existing teams. (Wilcoxon et al. 2011)

The efficacy of MDT's in informed clinical decision making, coordinated care and evidence-based practice for breast cancer patients has been well documented. (Prades et al. 2015, Taylor et al. 2013, Wong et al. 2014, McKeivitt et al. 2017) Several of the included studies in this review identified limited access to MDT care for non-metropolitan women as a possible contributor to lower receipt of guideline concordant care, (Roder et al. 2013c, Roder et al. 2013a, Roder et al. 2013b, Roder et al. 2012b, Dasgupta et al. 2017, Yu et al. 2015) It is possible that the major benefits of MDT lie, in part, with greater adherence to standard therapy, (Roder et al. 2012b, Yu et al. 2015, Taylor et al. 2013) which may indirectly impact clinical outcomes.

The evidence for the impact of MDT on breast cancer survival is more limited, possibly reflecting methodological limitations and heterogeneity in MDT definitions. (Rogers et al. 2017, Taylor et al. 2013) However, surgical specialization has been shown to be associated with improved survival, (Gooiker et al. 2010) and we found that non-metropolitan women had consistently poorer access to high-volume surgeons (Mitchell et al. 2006, Roder et al. 2013c, Roder et al. 2013b, Baade et al. 2016) which in Australia are predominantly based in major cities. (AIHW 2017b)”

9. Supplementary files make up 2/3 of the submission and most could be deleted, briefly summarized, or offered to be sent on request.

Author's response: Given that this journal is an online journal, we would prefer to have this more detailed information as Supplementary files, and so readily available for readers.
No changes have been made to the manuscript

10. Pg.10. Very interesting findings: non-metropolitan women were at least five times more likely to have a mastectomy than metropolitan women. "Two studies based on the National Breast Cancer Audit Database reported that non-metropolitan women were up to 20% less likely to receive adjuvant radiotherapy than metropolitan women.^{42 61} Moreover women residing in areas lacking radiotherapy facilities had a higher likelihood (23%) of not receiving radiotherapy than those from regions with such facilities.⁶¹" suggests poverty is the issue.

Author's response: We have already discussed the impact of lack of access to radiotherapy on choice of surgical treatment in the Discussion. (Page 14) Additional commentary on the role of socio-economic disadvantage in these patterns has now been added. (Discussion, Page 14):
"Both service affordability and availability impact radiotherapy utilization (AIHW 2017c) with the uptake of breast conserving surgery among regional women increasing after provision of a publicly funded local radiotherapy service. (Lam et al. 2015) Similar patterns were also reported for radiotherapy utilization among all regional cancer patients. (Sharma et al. 2016, Butler 2017)"

11. Pg. 12, line 39. "...good evidence that poorer breast cancer survival for nonmetropolitan women reflects more advanced disease at diagnosis, greater comorbidities and treatment-related factors." Authors should cite sample of outstanding studies for these assertions.

Author's response: References to articles included in this review have been added to this sentence (Page 12, Discussion, Paragraph 2):
"While gaps in the literature limited our ability to draw clear links between identified variations and the drivers of these variations, there was good evidence that poorer breast cancer survival (at least up to five years after diagnosis) for non-metropolitan women reflects more advanced disease at diagnosis, greater comorbidities, treatment-related factors and area-disadvantage. (Cramb et al. 2012, Dasgupta et al. 2012, Mitchell et al. 2006, Roder et al. 2012a, Spilsbury et al. 2005, Supramaniam et al. 2014, Tracey et al. 2008, Tervonen et al. 2017)"

12. Pg. 13 multidisciplinary team is this supported by evidence?

Author's response: Additional commentary on the impact of multidisciplinary care on breast cancer outcomes has been added to the Discussion on Page 13.

Please see response to Comment#8

13. Pg. 14. Say what "Cancer Australia" is when the agency is first cited in the text.

Author's response: We state that Cancer Australia is Australia's national cancer control agency here and this is the first time this agency is cited.
No changes have been made to the manuscript

14. Pg. 14. Good paragraph but could more be found in this article's data base to move toward resolution of issues in the following paragraph: On an international scale, inequities in access to specialised care(Gentil et al. 2012, Albormoz et al. 2013, Kong et al. 2011) and geographical variations across the breast cancer continuum including screening,(Leung et al. 2014) stage at diagnosis(Nguyen-Pham et al. 2014, Olson et al. 2012) and patterns of care(Mac Bride et al. 2013, Ess et al. 2010, Zhong et al. 2014, Markossian et al. 2012, Olson et al. 2012, Dragun et al. 2011,

Hershman et al. 2012, Meilleur et al. 2013) are well documented. There is widespread consensus that these variations reflect a combination of socio-economic, demographic and environmental factors including geography, comorbidities, access, treatment and stage at diagnosis that defy easy solutions.(Nguyen-Pham et al. 2014, Gentil et al. 2012, Markossian et al. 2012, Olson et al. 2012, Kong et al. 2011, Leung et al. 2014, Meilleur et al. 2013) The persistence of such inequities even for universal (publicly-funded) health-care systems(Ess et al. 2010, Gentil et al. 2012, Zhong et al. 2014, Olson et al. 2012, Leung et al. 2014) highlights the complexity of the underlying issues.

Author's response: Additional commentary has been added about the potential for harnessing emerging technologies including teleoncology to promote coordinated care and facilitate the educational diffusion of health care innovations both to surgeons and patients, especially in non-metropolitan areas. (Page 16, Conclusions, Paragraph 2):

"To achieve equitable access for all women, it is crucial to promote coordinated care among non-metropolitan women and initiatives to facilitate the educational diffusion of health care changes among clinicians and patients through emerging technologies (Sabesan et al. 2014) to overcome barriers of distance."

Reviewer 2

15. It is not clear why this review had to be limited to an Australian setting, and I would prefer that it was not limited in this way. Certainly a large proportion of research has been done in Australia, but there are important studies from elsewhere that are interesting to this general area of research: rural vs urban outcomes in breast cancer.

Author's response: Our objective was to assess the geographical patterns along the breast cancer continuum of detection, diagnosis, treatment and survival. While we agree that including international studies would be useful, the number of studies that would need to be added to extend the scope of this review would make a single manuscript implausible. By restricting the review to the Australian setting, we are able to interpret the results within the population and health service delivery characteristics that are unique to Australia.

We also refer to the comment made by the Associate Editor along these lines.

For these reasons, no changes have been made to the manuscript

16. In the discussion, the rationale for radiotherapy is correctly (in part) described to reduce local recurrence, but the potential survival benefit of radiotherapy is not fully described or possibly associated with differences in outcomes. This should be added, as others (e.g. BC, Canada) have shown nodal radiotherapy is used less frequently in small, and rural locations, which could result in lower survival.

Author's response: Additional commentary has been added (Discussion, Page 14, Paragraph 2):

"Given the potential survival benefits of adjuvant radiotherapy, (Darby et al. 2011, Early Breast Cancer Trialists' Collaborative Group. 2014) the lower utilization of radiotherapy among non-metropolitan women (Azzopardi et al. 2014, Kok et al. 2006, Mitchell et al. 2006, Roder et al. 2013c) and those with poorer access to radiotherapy facilities (Azzopardi et al. 2014, Hsieh et al. 2015, Collins et al. 2017) is of concern."

17. A better description of socioeconomic differences across Australia would be helpful for non-local readers.

Author's response: Additional commentary has been added to the Introduction (Page 4, Paragraph 2):

"There is also considerable overlap between remoteness and socioeconomic status; around a third of the population living in major cities in Australia also live in areas classified as least disadvantaged, compared to only 2% of those from very remote areas. (AIHW 2007)"

18. Figures summarizing the differences in survival, screening rate, mastectomy use, adjuvant local radiotherapy, adjuvant loco-regional radiotherapy, adjuvant chemotherapy, adjuvant hormonal therapy use would help the reader get a better overall view of the differences.

Author's response: As noted previously in reference to the lack of a meta-analysis, the wide variety in methods and measures within the different indicators make comparisons of the quantitative measures impossible. However, as requested by Reviewer #1, we have included summary tables that are intended to provide a clearer overall view of the differences.

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VERSION 2 – REVIEW

REVIEWER	Robert Olson University of British Columbia, Canada
REVIEW RETURNED	04-Jan-2018
GENERAL COMMENTS	reasonable edits and acceptable for publication